Nonketotic Hyperosmolar Syndrome

GENERAL PRINCIPLES

Nonketotic hyperosmolar syndrome (NKHS) is one of the most serious life-threatening complications of T2DM.

Epidemiology

- Hyperosmolar hyperglycemic state (HHS) occurs primarily in patients with T2DM and in 30% to 40% of cases; NKHS is the initial presentation of a patient's diabetes (*Emerg Med Clin North Am 2005;23:629-648*).

- NKHS is significantly less common than DKA with an incidence of <1 case per 1,000 person-years.

Pathophysiology

- Ketoacidosis is absent because the ambient insulin level may effectively prevent lipolysis and subsequent ketogenesis yet is inadequate to facilitate peripheral glucose uptake and to prevent hepatic residual gluconeogenesis and glucose output.
- Precipitating factors include dehydration, stress, infection, stroke, noncompliance with medications, dietary indiscretion, and alcohol and cocaine abuse. Impaired glucose excretion is a contributory factor in patients with renal insufficiency or prerenal azotemia.

DIAGNOSIS

Clinical Presentation

In contrast to DKA, the onset of NKHS is usually insidious. Several days of deteriorating glycemic control are followed by increasing lethargy. Clinical evidence of severe dehydration is the rule. Some alterations in consciousness and focal neurologic deficits may be found at presentation or may develop during therapy. Therefore, repeated neurologic assessment is recommended.

Differential Diagnosis

The differential diagnosis of NKHS includes any cause of altered level of consciousness, including hypoglycemia, hyponatremia, severe dehydration, uremia, hyperammonemia, drug overdose, and sepsis. Seizures and acute stroke-like syndromes are common presentations.

Diagnostic Testing

Laboratories

Clinical findings include (a) hyperglycemia, often >600 mg/dL; (b) plasma osmolality >320 mOsm/L; (c) absence of ketonemia; and (d) pH > 7.3 and serum bicarbonate level of >20 mEq/L. Prerenal azotemia and lactic acidosis can develop. Although some patients will have detectable urine ketones, most patients do not have a metabolic acidosis. Lactic acidosis may develop from an underlying ischemia, infection, or other cause.

TREATMENT

- **The goals of therapy are as follows:**
  - Restoration of hemodynamic stability and intravascular volume by fluid replacement.
  - Correction of electrolyte abnormalities.
  - Gradual correction of hyperglycemia and hyperosmolarity with fluid replacement and insulin therapy.
  - Detection and treatment of underlying disease states and precipitating causes. However, such efforts should not delay fluid replacement and insulin therapy.
- **Initial treatment** can make a difference in the frequency of complications and outcome. Therapy must be individualized on the basis of the degree of dehydration and underlying cause (sepsis and renal and cardiac function). Rapid vein access and urinary catheterization are essential.

  - **Restoring hemodynamic stability** is the first aim. Restoration of intravascular volume should be followed by correction of total body water deficit. Compared to DKA, patients with NKHS may require as much as 10 to 12 L of positive fluid balance over 24 to 72 hours to restore total deficits.
  - **Electrolyte management**
    - Although the potassium level may be initially normal or even high, all patients with NKHS are potassium depleted. Rehydration and insulin therapy usually result in hypokalemia, and this should be corrected.
    - If the initial potassium levels are low, replacement should begin immediately after urine output is ensured. Lactic acidosis requiring bicarbonate therapy may develop as a complication of NKHS or metformin therapy.
  - **Insulin therapy.** Insulin plays a secondary role in the initial management of NKHS, and fluid therapy always should precede insulin administration.
    - In patients with marked hyperglycemia (>600 mg/dL), regular insulin, 5 to 10 units IV, should be given immediately, followed by continuous infusion of 0.1 to 0.15 units/kg/hr. Lower doses of a regular insulin bolus can be used for less severe hyperglycemia.
    - Once plasma glucose decreases to 250 to 300 mg/dL, insulin infusion can be decreased to 1 to 2 units/hr and 5% dextrose should be added to the IV fluids. After full rehydration and clinical recovery, regular insulin can be given SC and patients can thereafter resume their usual diabetes therapy.
- **Underlying illness.** Detection and treatment of any underlying predisposing illness are critical in the treatment of NKHS. Antibiotics should be administered early, after appropriate cultures, in patients in whom infection is known or suspected as a precipitant to a HHS. A high index of suspicion should be maintained for underlying pancreatitis, GI bleeding, renal failure, and thromboembolic events, especially acute MI.

COMPLICATIONS

Complications of NKHS include thromboembolic events (cerebral and MI, mesenteric thrombosis, pulmonary embolism, and disseminated intravascular coagulation), cerebral edema, adult respiratory distress syndrome, and rhabdomyolysis.

MONITORING/FOLLOW-UP

- **Monitoring of therapy.** Use of a flowchart is helpful for tracking clinical data and laboratory results.
- Initially, BG levels should be monitored every 30 to 60 minutes and serum electrolyte levels every 1 to 2 hours; frequency of monitoring can be decreased during recovery.
- Neurologic status must be reassessed frequently; persistent lethargy or altered mentation indicates inadequate therapy. On the other hand, relapse after initial improvement in mental status suggests too-rapid correction of serum osmolarity.